



## General

### Guideline Title

Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline.

### Bibliographic Source(s)

Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, Cuzick J, Davidson NE, DeCensi A, Fabian C, Ford L, Garber J, Katapodi M, Kramer B, Morrow M, Parker B, Runowicz C, Vogel VG 3rd, Wade JL, Lippman SM. Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013 Aug 10;31(23):2942-62. [65 references]  
[PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Visvanathan K, Chlebowski RT, Hurley P, Col NF, Ropka M, Collyar D, Morrow M, Runowicz C, Pritchard KI, Hagerty K, Arun B, Garber J, Vogel VG, Wade JL, Brown P, Cuzick J, Kramer BS, Lippman SM, American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *J Clin Oncol*. 2009 Jul 1;27(19):3235-58.

## Recommendations

### Major Recommendations

*Note from the American Society of Clinical Oncology (ASCO) and the National Guideline Clearinghouse (NGC):* Table 1 in the original guideline document (see the "Guideline Availability" field) contains a comparison between the 2009 recommendations and the new recommendations, as well as the strength of recommendation and strength of evidence for each recommendation.

#### Clinical Question

Which pharmacologic interventions reduce the risk of developing breast cancer in women not previously diagnosed with breast cancer?

Selective Estrogen Receptor (ER) Modulators (SERMs)

#### *Tamoxifen Recommendation*

Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal and postmenopausal women who are age  $\geq 35$  years with a 5-year projected absolute breast cancer risk  $\geq 1.66\%$ , according to the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (or equivalent measures), or with lobular

carcinoma in situ (LCIS). The risk reduction benefit continues for at least 10 years in both premenopausal and postmenopausal women. Tamoxifen is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Tamoxifen is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers. Tamoxifen is not recommended in combination with hormone therapy. Follow-up while on tamoxifen should include a timely workup of abnormal vaginal bleeding. Discussions with patients by health care providers should include both the risks and benefits of tamoxifen.

#### *Raloxifene Recommendation*

Raloxifene (60 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women who are age  $\geq 35$  years with a 5-year projected absolute breast cancer risk  $\geq 1.66\%$ , according to the NCI Breast Cancer Risk Assessment Tool (or equivalent measures), or with LCIS. Raloxifene may be used longer than 5 years in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit. Raloxifene should not be used for breast cancer risk reduction in premenopausal women and is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Discussions with patients by health care providers should include both the risks and benefits of raloxifene.

#### *Aromatase Inhibitors*

##### *Exemestane Recommendation*

Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age  $\geq 35$  years with a 5-year projected breast cancer absolute risk  $\geq 1.66\%$ , according to the NCI Breast Cancer Risk Assessment Tool (or equivalent measures), or with LCIS or atypical hyperplasia. Exemestane should not be used for breast cancer risk reduction in premenopausal women. Discussions with patients and health care providers should include both the risks and benefits of each agent under consideration.

Of note, exemestane is U.S. Food and Drug Administration (FDA) approved only for the adjuvant treatment of early breast cancer and the treatment of advanced breast cancer, not for breast cancer risk reduction

([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020753s009s011s012lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020753s009s011s012lbl.pdf) ).

##### *Anastrozole Recommendation*

The Update Committee concluded that there was insufficient evidence to provide a recommendation for anastrozole to guide clinical practice.

## Clinical Algorithm(s)

None provided

## Scope

### Disease/Condition(s)

Breast cancer

### Guideline Category

Prevention

Risk Assessment

Technology Assessment

Treatment

# Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Preventive Medicine

## Intended Users

Physicians

## Guideline Objective(s)

- To update the 2009 American Society of Clinical Oncology guideline on pharmacologic interventions for breast cancer risk reduction
- To address the following clinical issues:
  - Whether pharmacologic interventions, tested in phase III randomized controlled trials (RCTs), reduce the risk of developing breast cancer (invasive or noninvasive) compared with no pharmacologic interventions
  - The comparative efficacy of the breast cancer chemoprevention agents
  - What constitutes effective and responsible communication by physicians of issues regarding breast cancer risk reduction

## Target Population

Women without a personal history of breast cancer who are at increased risk of developing the disease

## Interventions and Practices Considered

1. Selective estrogen receptor modulators (SERMs):
  - Tamoxifen
  - Raloxifene
2. Aromatase inhibitors: exemestane

Note: Anastrozole was considered but not recommended.

## Major Outcomes Considered

- Breast cancer incidence (invasive and noninvasive)
- Breast cancer mortality
- Adverse events
- Net health benefits

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

## Description of Methods Used to Collect/Select the Evidence

### Literature Review and Analysis

#### Literature Search Strategy

The Update Committee completed a systematic review and analysis of the literature published since the 2009 guideline update. The Update Committee's literature review focused attention on available systematic reviews and meta-analyses of published phase III randomized controlled trials (RCTs) on breast cancer risk reduction. Literature searches of MEDLINE and the Cochrane Collaboration Library were performed. Searches of the English language literature from June 2007 through June 2012 were conducted to address each of the guideline recommendations. The searches were supplemented with the references of the selected articles as well as references provided by guideline Update Committee members. A summary of the literature review results is provided in a Quality of Reporting of Meta-Analyses (QUOROM) diagram in the online Data Supplement Table DS7 (available at <http://www.asco.org/guidelines/bcrr> ; see also the "Availability of Companion Documents" field).

#### Inclusion and Exclusion Criteria

Searches were limited to phase III RCTs, meta-analyses, systematic reviews, and existing clinical practice guidelines. Retrospective cohort studies were permitted if they were embedded within an RCT. Other study designs, including prospective or retrospective cohort studies and phase I or II trials, were excluded. English-language studies available in full text and published in peer-reviewed journals were eligible. Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the intervention consisted of one of the specified chemoprevention agents for the prevention of primary breast cancer; (2) participants were randomly assigned to a chemoprevention arm or a control arm (control arm could consist of no chemoprevention agent, a placebo, the same chemoprevention agent at an alternate dose/route, or a different chemoprevention agent); and (3) outcomes reported included at least one of the following: breast cancer incidence, breast cancer-specific mortality, overall mortality, net health benefits, or quality of life. The primary outcome of interest was incidence of invasive and noninvasive breast cancer (including ductal carcinoma in situ). The guideline is limited to pharmacologic interventions, and therefore, evaluations of surgical and lifestyle interventions were excluded from consideration. The Update Committee Co-Chairs reviewed the title lists of included and excluded abstracts, and full text articles were obtained for each included abstract.

## Number of Source Documents

Nineteen articles met the selection criteria.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Ratings for the Strength of the Total Body of Evidence

Rating	Definition
Strong	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Moderate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Weak	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Rating	Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.
	Definition

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Data Extraction

Data were extracted from each article that met the inclusion criteria for patient and study characteristics, study quality, interventions, outcomes, and adverse events. Evidence tables were developed based on data extracted from these studies. A Data Supplement includes additional tables and figures (see the "Availability of Companion Documents" field). Data were extracted by one reviewer and subsequently checked independently for accuracy by a second reviewer. Disagreements were resolved by discussion and/or by consultation with Update Committee Co-Chairs, if necessary.

Study Quality and Limitations of the Literature

Although all of the trials were RCTs, there was heterogeneity across them on key elements, such as participant and disease characteristics. Table DS10 in the online Data Supplement (see the "Availability of Companion Documents" field) presents a summary of key quality and design elements and a rating of the overall risk of bias for each study. The overall risk of bias for all of the studies was considered low.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee convened an Update Committee of experts in clinical medicine, public health, clinical research, health services, and related areas (i.e., biostatistics, epidemiology, cancer prevention, patient-physician communication) with expertise in breast cancer prevention, along with a patient representative.

Guideline Development Process

The Update Committee held a teleconference in June 2012 to review the evidence and draft the guideline recommendations. Before the teleconference, the Update Committee members were sent evidence tables for review and were asked to complete an online survey about the content of the recommendations. During the teleconference, the Committee discussed the evidence and issues for each agent and the content of the recommendations. After the teleconference, a draft of the recommendations was sent to the entire Update Committee for comments. Any contentious comments or questions raised were addressed by e-mail until agreement was reached by the Committee. Additional work on the guideline document was completed through a steering group and by e-mail. All members of the Update Committee participated in the preparation of the draft guideline document and reviewed and approved the final guideline document.

## Rating Scheme for the Strength of the Recommendations

Ratings for the Strength of Recommendations

Rating for Strength of Recommendation	Definition

Strong Rating for Strength of Recommendation	Definition There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

## Cost Analysis

A formal cost analysis was not performed and published cost analysis were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

The guideline was submitted to *Journal of Clinical Oncology* for peer review. Feedback was also solicited from external reviewers. Before publication, the guideline was reviewed and approved by the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see Table 1 in the original guideline document for the strength of recommendation and strength of evidence for each recommendation).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate management of women at increased risk of breast cancer

### Potential Harms

Tamoxifen

Serious adverse events associated with tamoxifen use include endometrial cancer, stroke, transient ischemic attack, venous thromboembolism, deep vein thrombosis, and pulmonary embolism. Two studies have also identified specific subgroups of women at increased risk of developing

venous thromboembolism while on tamoxifen: women who are immobilized in the prior 3 months and/or women who have body mass index (BMI)  $>25 \text{ kg/m}^2$ .

#### Raloxifene

Raloxifene is associated with a more favorable adverse effect profile compared with tamoxifen including a significantly lower risk of thromboembolic disease (statistically significant only for deep vein thrombosis) and uterine cancer and lower incidence of benign uterine hyperplasia, cataracts, and cataract surgery.

#### Exemestane

- Table 6 in the original guideline document summarizes the key findings for adverse events in the MAP.3 trial. Overall, more adverse events occurred in the exemestane group compared with the placebo group of the MAP.3 trial. There were no statistically significant differences in the incidence of serious adverse events including cardiovascular events, skeletal fractures, other cancers, or treatment-related deaths. Statistically significant differences were observed for endocrine-related adverse events (i.e., hot flashes, fatigue, sweating, insomnia), constitutional and gastrointestinal (GI) events (i.e., diarrhea and nausea), and joint and muscle pain.
- Results from a post hoc nested substudy of the MAP.3 trial demonstrated a statistically significant reduction in bone mineral density and cortical thickness at the distal tibia and distal radius, lumbar spine, total hip, and femoral neck. Compared with placebo, 2 years of treatment with exemestane worsened age-related bone loss in postmenopausal women, despite calcium and vitamin D supplementation.
- Minimal differences in quality-of-life outcomes were observed between the exemestane and placebo groups. There was a statistically significant increase in the incidence of vasomotor symptoms, bodily pain, and sexual problems in women who took exemestane compared with women in the placebo group.

Tables 3-6 in the original guideline document contain information on adverse events and side effects related to tamoxifen, raloxifene, and exemestane.

## Contraindications

### Contraindications

- Neither tamoxifen nor raloxifene is recommended for use in women with a personal history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization, because of the increased risk of adverse events in these women.
- Tamoxifen is not recommended for use in women who are, or may become, pregnant, or nursing mothers.
- Neither raloxifene nor exemestane is recommended for use in premenopausal women.

## Qualifying Statements

### Qualifying Statements

#### Guideline Policy

This practice guideline is not intended to substitute for the independent professional judgment of the treating physician. This practice guideline does not account for individual variation among patients and may not reflect the most recent evidence, because it is bound by the date parameters of the systematic review. This guideline does not recommend any particular product or course of medical treatment. Use of this practice guideline is voluntary.

#### Study Quality and Limitations of the Literature

Although all of the trials were randomized controlled trials (RCTs), there was heterogeneity across them on key elements, such as participant and disease characteristics. Table DS10 in the online Data Supplement (see the "Availability of Companion Documents" field) presents a summary of key quality and design elements and a rating of the overall risk of bias for each study. The overall risk of bias for all of the studies was considered low.

# Implementation of the Guideline

## Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the [ASCO Web site](#)

## Implementation Tools

Patient Resources

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Staying Healthy

### IOM Domain

Effectiveness

Patient-centeredness

Safety

## Identifying Information and Availability

### Bibliographic Source(s)

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### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released



## Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

## Source(s) of Funding

American Society of Clinical Oncology (ASCO)

## Guideline Committee

American Society of Clinical Oncology (ASCO) Breast Cancer Risk Reduction Guideline Update Committee

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

The Update Committee was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflict of Interest Management Procedures for Clinical Practice Guidelines (Procedures, summarized at <http://www.asco.org/guidelinescoi> ). Members of the Update Committee completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors. Authors marked with an asterisk (\*) are participants in ASCO's Disclosure Management System Pilot; their disclosure is not limited to subject matter under consideration in this article and includes payments to themselves, an immediate family member (I), and/or their institutions (INST).

Employment or Leadership Position: None Consultant or Advisory Role: Judy Garber, Novartis (C), Pfizer (C) \*Carolyn Runowicz, Bayer (C), Champions Biotechnology (C) Stock Ownership: James L. Wade, Novartis Honoraria: Jack Cuzick, AstraZeneca Research Funding: Jack Cuzick, AstraZeneca; Judy Garber, AstraZeneca, Novartis, Pfizer Expert Testimony: None Patents: None Other Remuneration: None

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## Guideline Availability

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: [guidelines@asco.org](mailto:guidelines@asco.org)

## Availability of Companion Documents

The following are available:

- Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2013. 16 p. Electronic copies: Available in Portable Document Format (PDF) from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .
- Breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2013. 31 p. Electronic copies: Available in PDF  and PowerPoint format  from the ASCO Web site.
- Medications to reduce the risk of developing breast cancer: American Society of Clinical Oncology clinical practice guideline. Decision aid tool. Alexandria (VA): American Society of Clinical Oncology; 2013. 2 p. Electronic copies: Available in PDF from the [ASCO Web site](#) .

## Patient Resources

The following are available:

- Drugs to lower breast cancer risk. Alexandria (VA): American Society of Clinical Oncology; 2013. Electronic copies: Available from the [Cancer.net Web site](#) . Also available as a Podcast from the [Cancer.net Web site](#) .
- Lowering your risk of breast cancer. Infographic. Alexandria (VA): American Society of Clinical Oncology; 2013. 1 p. Electronic copies: Available from the [Cancer.net Web site](#) .

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## NGC Status

This NGC summary was completed by ECRI on February 27, 2003. The information was verified by the guideline developer on March 14, 2003. This NGC summary was updated by ECRI Institute on January 27, 2010. This NGC summary was updated by ECRI Institute on October 14, 2013.

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